NEW USE OF GLUCOSE AND A NEW SOLUTION OF GLUCOSE

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Abstract

Glucose, fructose and/or xylose are suggested to be used for the preparation of an infusion solution intended for preoperative administration. An infusion solution is disclosed, which in addition to glucose, fructose and/or xylose and potassium chloride also contains glutamine and/or ornithine-alfa-ketoglutarate or the corresponding glutamine analogues which are transformed into glutamine in the body and possibly one or more hormones. Furthermore, a method is disclosed for suppressing the negative influence of an operation on patient carbohydrate metabolism after surgery and improving the defence capacity of the patient on bleeding in connection with or after the operation which method comprises preoperative intravenous administration to the patient of an infusion solution containing at least one carbohydrate selected from the group consisting of glucose, fructose and xylose.

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(57) Abstract

Glucose, fructose and/or xylose are suggested to be used for the preparation of an infusion solution intended for preoperative administration. An infusion solution is disclosed, which in addition to glucose, fructose and/or xylose and potassium chloride also contains glutamine and/or ornithine-alfa-ketoglutarate or the corresponding glutamine analogues which are transformed into glutamine in the body and possibly one or more hormones. Furthermore, a method is disclosed for suppressing the negative influence of an operation on patient carbohydrate metabolism after surgery and improving the defence capacity of the patient on bleeding in connection with or after the operation which method comprises preoperative intravenous administration to the patient of an infusion solution containing at least one carbohydrate selected from the group consisting of glucose, fructose and xylose.

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NEW USE OF GLUCOSE AND A NEW SOLUTION OF GLUCOSE

The present invention relates to a new use of glucose, fructose and/or xylose and an infusion solution intended for preoperative administration. The invention also relates to a method of suppressing the negative influence on the metabolism of carbohydrates caused by surgery and improving the defence capacity of the patient upon bleeding during or after the operation.

Elective surgical (i.e. not acute) operations are yearly carried out at a number of approximately 2-300000 in Sweden alone. A routine operation always brings about a relatively long period (weeks) of convalescence for physical recovery. Routinely all patients planned for surgery undergo a period of fasting before the operation, usually from midnight to the day of surgery. The effective period of fasting, however, becomes at least 16-20 h because the last meal of food generally is served around 16.00 h. The obligatory fast before surgery has been introduced for reasons of safety related to anaesthesia and has not been considered to bring about negative effects for the patient.

However, a considerable change in body metabolism occurs already during the period of preoperative fasting. Most important is the fact that the reserves of carbohydrates in the body (primarily glycogen in the liver) are consumed. The requirements of the brain of glucose, however, remains unchanged for some additional days. To meet this demand for glucose, the body metabolism is changed, so that new glucose can be produced. Glucose production is accomplished by degradation of glucose and fat reserves (in muscle and fat tissue), and by degradation of protein in muscle. Thereby, amino acids (alanine and glutamine and others) are released and transported to the liver for new glucose formation. Of particular interest is that the bowel for its meta-

bolism, to a large extent is dependent on the amino acid glutamine. Normally, glutamine is supplied by means of the food intake, but during fasting (and to a greater extent after trauma) the glutamine requirements of the bowel is supplied via degradation of glutamine stored in the proteins of the muscles. In order to enable the degradation of the energy depots of the body to take place, the release of hormones in the body must change. By changes in hormone release, the body thus changes from storage of nutrients (anabolism) to degradation of nutrients (catabolism). This shift in body metabolism forms a normal part of metabolism and occurs already during normal overnight sleep. When the first meal of the day is ingested, the body responds by activating specific hormones (primarily insulin) to ensure the storage of the received energy of carbohydrates, protein and fat.

Thus already preoperative fasting leads to two essential changes in the metabolism of carbohydrates:

1. consumption of glucose reserves, and
2. changes in metabolism

These changes in the metabolism of carbohydrates in the body has important consequences for the immediate response to stress, as well as for the recovery after stress and surgery.

It has been documented that a reduction of the carbohydrate reserves (glycogen) in the liver, which occurs already after a brief period of fasting (6-24 hours in the rat and man), brings about increased mortality in experimental haemorrhage and endotoxaemia. In experiments of haemorrhage in rats, it has been proven that the glycogen of the liver is rapidly mobilized (as glucose) to the blood circulation, where markedly increased glucose levels could be registered. The increase in blood glucose thus obtained,

actively participates in the blood volume preservation by mobilizing fluid by osmosis from the large fluid reserve located within the body cells to the circulation. Already after a short period of fasting (hours), this potential for fluid mobilization is decreased. This mechanism for fluid defense exists in the majority of mammals, including man. The preoperative fast accordingly causes a considerable reduction in the potential to maintain adequate circulation (e.g. blood volume) in case of bleeding during or after surgery.

In all types of stress (including surgery) body metabolism is rapidly changed into a state, where the normal balance between catabolic and anabolic processes is strongly displaced towards catabolism. The most important factor known for this change to develope is a major reduction of the effects of insulin (which is the most important hormone known for storage of nutrients). This condition is often called stress-induced insulin resistance. It has been proven that the degree of insulin resistance developing after elective surgery is increased with the magnitude of surgery (i.e. small operations result in lesser degrees of insulin resistance compared to greater surgery). Furthermore, the insulin resistance after surgery persists for a long period of time and a normalization is found after approximately three weeks. As long as insulin resistance remains, the body has difficulties in recovering. Therefore, it is desirable to reduce the magnitude of insulin resistance after surgery as well as restoring the sensitivity of insulin as soon as possible. Essential for this recovery is a return to normal metabolism of carbohydrates. The brain, blood cells and other cells are completely dependent on carbohydrates (e.g. glucose) for their metabolism, whereas muscle require a certain minimum of supply of carbohydrates for their function. A simple way of reducing the degree of insulin re-

sistance after surgery, and thus improving postoperative carbohydrate metabolism, has not been described in literature.

The present invention is based on the finding that it was possible by preoperative administration of a solution containing glucose not only to improve the body's capacity of the patient to withstand blood loss during or after surgery but also to improve postoperative carbohydrate metabolism by reducing the degree of insulin resistance after the operation.

As far as it is known to-day, there has been no literature that has been able to prove these effects by preoperative supply of solutions containing glucose. The effect of preoperative administration of glucose on postoperative metabolism has been studied only in one previous investigation (Crowe et al., British J. Surg. 1984. 71; 635-637). The investigation was specifically directed to postoperative metabolism of proteins, by measuring the excretion of urea and 3-methylhistidine/creatinine index in the urine. However, the investigation has serious scientific defects. The investigation was not randomized, and it is not evident what operations were performed in the different groups of patients. In view of the fact that the magnitude of surgery is directly decisive for the responses of the body, it must be considered very difficult to draw any conclusions from this investigation. The authors own conclusion was that preoperative glucose supply possibly could be of use for postoperative metabolism of proteins, but there is no suggestion whatsoever that this pretreatment could bing about favourable effects for the metabolism of carbohydrates, nor that such treatment could decrease the risks in case of bleeding complicating surgery.

More particularly, the present invention is based on the following findings:

1. Experiments on animals.

Survival after 42 % blood loss in rats fasted for 24 h was compared after treatment with either 30 mg/ml glucose, 0.3 ml/kg body weight/h, intravenously, or after the same volume of 0.9 % NaCl given during 3 h before the start of haemorrhage. Ten animals were included in each of the treatment groups, glucose (G) or saline (S), and subjected to 60 min of haemorrhage. Twelve additional animals (6 G and 6 S) were sacrificed after infusion for determination of liver glycogen content. Glucose treated rats had 578 ± 72 μmol/g dry liver weight (mean ± SE) of glycogen compared to 104 ± 32 μ mol/g, significance $p < 0.01$ (Mann Whitney U-test). After haemorrhage, G had blood glucose levels of 16.1 ± 0.9 mmol/l compared to S 5.2 ± 0.1, $p < 0.01$. This increase in blood glucose in group G resulted in improved fluid mobilization to the circulation, as indicated by a lower haematocrit in group G (35 ± 1 %) versus group S (40 ± 1 %), $p < 0.01$. While all animals pretreated with saline had died within 4 h after completion of haemorrhage, all animals given glucose prior to haemorrhage recovered completely after haemorrhage (7 days of observation).

The hormonal response on bleeding was investigated in two groups of rats pretreated according to the protocol described above. Rats pretreated with glucose showed a hormone response with increased insulin levels in the blood in a way which previously has been observed only in not fasted animals and subjected to haemorrhage. This insulin release is not found in 24 h fasted (and untreated) rats, nor could it be reproduced by treatment initiated once the bleeding had been started.

2. Clinical experiments.

In 12 patients, healthy apart from gallstone and operated electively for cholecystectomy, were randomly allocated into receiving either glucose 5 mg/kg/min intravenously from 6.00 pm the day before operation until start of surgery, or no infusion during this period (e.g. routine fasting period). Insulin sensitivity (M-value) was determined using the euglycemic hyperinsulinemic clamp techniques within 3 days prior to surgery, and on the first post-operative day. Pre-operative M-values were similar in both groups (n = 6); 4.64 ± 1.36 mg/kg/min in glucose treated patients and 4.31 ± 0.35 mg/kg/min in fasted patients, difference not significant. Postoperative M-value the day after surgery was significantly ($p < 0.02$) lower in fasted patients (2.00 ± 0.21 mg/kg/min) compared to patients pretreated with glucose (3.14 ± 0.88 mg/kg/min). This finding shows that pretreatment with glucose infusion during preoperative fasting, significantly reduces the postoperative disturbance in carbohydrate metabolism.

Patients operated for gallstone desease have been pretreated with either glucose in infusion (5 mg/kg/min) during preoperative fasting or traditional fasting before the same operation. Under operation small pieces of liver tissue have been taken for analysis of the content of glucose (glycogen) as well as of the activity of enzymes involved in the control of the metabolism of carbohydrates in the liver. Patients treated with glucose showed higher contents of glycogen at the same time as the enzymatic setting was adjusted in a way which is more associated with that seen after a meal (than the one seen after fasting) compared to patients which have fasted.

This difference in hepatic enzymatic adjustment has experimentally been shown to be associated with marked diffe-

rences in post-stress metabolism. Enzymatic adjustment, such as that found after food intake was associated with improved post-stress carbohydrate metabolism.

In accordance with the above the present invention relates to the use of at least one carbohydrate selected from the group consisting of glucose, fructose and zylose, preferably glucose, for the preparation of an infusion solution intended for preoperative administration in order to suppress the negative influence of the operation upon postoperative carbohydrate metabolism and to improve the defence capacity of the patient in case of bleeding in connection with or after the operation without anaestesiological safety being jeopardized.

The content of glucose etc. in the infusion solution is suitably within the range which usually is used in nutrient solutions for intravenous supply of nutrients to patients which can not support themselves after surgery, for instance within the range from 50 g/l to 500 g/l, preferably 100 g/l to 200 g/l.

According to a preferred embodiment of the invention the infusion solution in addition to the glucose also contains potassium chloride. The content is also in this case suitably within the range which is usually occurring in solutions for nutrient supply after surgery. For instance the content of potasium chloride may be in the range from 20 mmol/l to 100 mmol/l, preferably about 40 mmol/l.

According to another embodiment of the invention the infusion solution may in addition to glucose and possibly potassium chloride also contain at least one of the substances fructose and xylose. The content of fructose or xylose or mixture thereof is suitably within the range from 50 g/l to 200 g/l, preferably 50 g/l to 100 g/l.

According to a further embodiment of the invention the infusion solution may in addition to glucose and possibly potassium chloride and/or fructose and/or xylose also contain glutamine and/or ornithine-alfa-ketoglutarate or corresponding glutamine analogues which in the body are converted to glutamine. By supplying glutamine and/or corresponding glutamine analogues which in the body are converted to glutamine, the body reserves of glutamine in the body are increased instead of decreased during the period of preoperative fasting. This improvement of availability of body glutamine will reduce the need for muscle protein breakdown for the release of glutamine, which is otherwise encountered after surgery. This, in turn, can improve postoperative muscle function. The content of glutamine etc. is suitably within the range 5 g/l to 30 g/l, preferably 10 g/l to 20 g/l.

According to still another embodiment of the invention the infusion solution may in addition to glucose and possibly potassium chloride and possibly one or more of the previously mentioned additional substances also contain one or more hormones such as an insulin or insulin derivative which is suitable for administration to man. In this case the content is adjusted so that a suitable dose of insulin is given with the infused amount of solution.

Examples of suitable insulins and insulin derivatives in this connection is human insulin such as Humilin NPH (Lilly) or Actrapid® Human (Novo).

Although insulin is the most important hormone for the normal storage of nutrients, other hormones and peptides also have anabolic effects on body metabolism. Thus, growth hormone, insulin growth factor as well as GLIP have been suggested to have insulin like effects. By supplying one or more of these preopratively, the body

metabolism is further adjusted to an anabolic state, which may prove beneficial for body reactions during and after surgery.

In addition to the mentioned additives the infusion solution may also contain other substances which are occurring in nutrient solutions for intravenous administration, if desired.

The infusion solution is drawn into glass bottles or plastics bags of 500 ml - 2000 ml. During the period of fast before the operation, from about 18.00 the day before the operation to the start of operation, the patient is given glucose 3-5 mg/kg/min intravenously (corresponding to about 60-100 ml/h 20 mg/ml glucose solution to a patient weighing 70 kg). The solutions can be packed up in different sizes in order to correspond to the need of patients of different weights.

According to another aspect of the invention this is related to an infusion solution, which is characterized in that it in addition to at least one carbohydrate selected from the group consisting of glucose, fructose and xylose, preferably glucose, and potassium chloride also contains ornitnine-alfa-ketoglutarate and/or glutamine and possibly one or more hormones. Such a solution for preoperative use has not been disclosed or suggested previously as far as we know.

According to still another aspect of the invention this is related to a method for suppressing the negative influence upon the metabolism of carbohydrates caused by an operation of a patient and improving the defence capacity of the patient on bleeding in connection with or after the operation which method comprises preoperative intravenous administration of the patient of an infusion solution containing at least one carbohydrate selected from

the group consisting of glucose, fructose and xylose, preferably glucose.

The invention will be illustrated further in the following by means of a number of working examples to which however the invention should not be limited.

EXAMPLE 1

An infusion solution is prepared in a conventional way for the preparation of infusion solutions, which infusion solution contains glucose (200 mg/ml) and potassium chloride (40 mmol/l) and the solution is drawn into volumes of 1500 ml.

In this way a package adjusted to a patient body weight of 70 kg is obtained which is to be administered during preoperative fastening to a patient which is healthy except the complaint for which the patient is to be operated.

EXAMPLE 2.

An infusion solution is prepared in a way conventional to the preparation of infusion solutions, which solution contains glucose (200 mg/ml), potassium chloride (40 mmol/l) and human insulin (Actrapid® Human, Novo, Denmark, 20 IE/l) and the solution is drawn into volumes of 1300 ml.

In this way a package adjusted to a patient body weight of 60 kg is obtained, which is to be administered during preoperative fastening to a patient with diabetes mellitus.

EXAMPLE 3.

An infusion solution is prepared in a way conventional to the preparation of infusion solutions, which solution con-

tains glucose (150 mg/ml), fructose (50 mg/ml) and potassium chloride (40 mmol/l), and the solution is drawn into volumes of 1200 ml.

In this way a package adjusted to patient body weight is obtained, which is to be administered during preoperative fasting to a patient weighing about 50 kg.

EXAMPLE 4.

An infusion solution is prepared in a way conventional to the preparation of infusion solutions, which solution contains glucose (200 mg/ml), ornithine-alfa-ketoglutarate (10 mg/ml) and potassium chloride (40 mmol/l), and the solution is drawn into volumes of 1500 ml.

In this way a package adjusted to patient body weight is obtained which is to be administered under preoperative fastening to a patient having a weight of about 70 kg.

The best mode for carrying out the invention at present comprises the preoperative administration of an infusion solution comprising glucose and potassium chloride dissolving water.

C L A I M S

1. The use of at least one carbohydrate selected from the group consisting of glucose, fructose and xylose, preferably glucose, for the preparation of an infusion solution intended for preoperative administration in order to suppress the negative influence of the operation upon the carbohydrate metabolism and to improve the defence capacity of the patient in case of bleeding in connection with or after the operation.

2. Use according to claim 1, characterized in that the infusion solution also contains potassium chloride.

3. Use according to claim 1 and/or 2, characterized in that the infusion solution in addition to glucose also contains at least one of the substances fructose and xylose.

4. Use according to one or more of claims 1 - 3, characterized in that the infusion solution also contains glutamine and/or ornithine-alfa-ketoglutarate or corresponding glutamine analogues which are transformed into glutamine in the body.

5. Use according to one or more of claims 1 - 4, characterized in that the infusion solution also contains one or more hormones, preferably an insulin or insulin derivative suitable for administration to man.

6. Infusion solution for preoperative administration, characterized in that it consists of an aqueous solution of at least one carbohydrate selected from the group consisting of glucose, fructose and xylose, preferably glucose, and potassium chloride together with glutamine and/or ornithine-alfa-ketoglutarate or the corresponding glutamine analogu s which are transformed into glutamine in the body and possibly one or more hormones.

7. Infusion solution according to claim 6, characterized in that the content of glutamine and/or ornithine-alfa-ketoglutarate or corresponding glutamine analogues which are transformed into glutamine in the body of the solution is 5-30 g/l, preferably 10-20 g/l.

8. Method for suppressing the negative influence of an operation on a patient carbohydrate metabolism after surgery and improving the defence capacity of the patient on bleeding in connection with or after the operation, which method comprises preoperative intravenous administration to the patient of an infusion solution containing at least one carbohydrate selected from the group consisting of glucose, fructose and xylose, preferably glucose.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00376

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K, 31/70, A 61 K 9/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	Patent Abstracts of Japan, Vol 10, No 182, C356, abstract of JP 61- 30523, publ 1986-02-12 Terumo Corp --	1-7
A	Patent Abstracts of Japan, Vol 10, No 252, C369, abstract of JP 61- 78719, publ 1986-04-22 Tanabe Seiyaku Co Ltd --	1-7

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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29th August 1991	1991 -09- 02
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Anneli Jönsson

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 91/00376

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent ffice EDP file on 91-06-27
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